

Report Documentation Page				Form Approved OMB No. 0704-0188	
Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number.					
1. REPORT DATE 01 JUN 2008		2. REPORT TYPE N/A		3. DATES COVERED -	
4. TITLE AND SUBTITLE A treatment worth its salt?				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Dubick M. A.,				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX 78234				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release, distribution unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 40	19a. NAME OF RESPONSIBLE PERSON
a. REPORT unclassified	b. ABSTRACT unclassified	c. THIS PAGE unclassified			

A treatment worth its salt?*

A new era in the treatment of shock began with the 1980 report that hypertonic (7.5%) saline (HS) could resuscitate dogs in hemorrhagic shock (1). This study sparked numerous investigations into the benefits of HS either alone or with dextran or hetastarch to resuscitate experimental animals from hemorrhagic hypotension (cited in Ref. 2) and led to several clinical trials in patients with traumatic hypotension (3–5). Other studies investigated the efficacy of these fluids in traumatic brain injury or intracranial hemorrhage (5, 6). These studies provided solid evidence for the physiologic effects of hypertonic fluids on expanding plasma volume and improving cardiac output, regional blood flows, and the microcirculation.

Sprinkled among the earlier studies were a few from the 1980s and early 1990s that investigated whether the hemodynamic effects of HS would be useful as supportive therapy in the treatment of sepsis in experimental animals (7–9). However, in the past decade recognition of possible immunomodulating effects of HS has opened new possibilities that the benefits of HS could extend beyond its hemodynamic effects. Hypertonicity was shown to inhibit leukocyte adherence and activation. Subsequent to improved microcirculatory flow, use of hypertonic fluids was associated with a reduction of neutrophils rolling and sticking to the endothelial cells of blood vessels (10–12). In addition, in isolated neutrophils from healthy human volunteers, it was observed that HS alone or with dextran inhibited their respiratory burst and decreased β_2 -integrin expression, superoxide production, and elastase release, but only if HS was added before neutrophils became primed or activated (10–14). How-

ever, if HS was added after neutrophil priming or activation, superoxide production and elastase release were actually enhanced (13). Immunomodulatory effects of HS have since been investigated in animal models of hemorrhage. Pascual et al. (12) observed that infusion of HS reduced neutrophil adherence to pulmonary endothelium and reduced lung myeloperoxidase activity compared with infusion of lactated Ringer's solution. These authors also reported that the susceptibility to sepsis after hemorrhage was diminished, possibly due to inhibition of sepsis-induced P-selectin expression or to bacterial challenge. Taken together, these data suggested that modulation of immune function by HS could possibly reduce secondary complications of infection and that initial or early hypertonic saline resuscitation would be of greater benefit than infusion after administration of conventional fluids. A similar conclusion that hypertonic fluids should be the initial resuscitation fluid was also drawn from the hemorrhage studies in experimental animals (2).

In this issue of *Critical Care Medicine*, Dr. Shih and colleagues (15) present a well-designed, comprehensive investigation of the use of HS vs. normal saline in a peritonitis-induced (cecal ligation and puncture [CLP]) septic shock model in rats. HS was infused 3 hrs after CLP. The investigators monitored standard hemodynamics and the systemic pressor response to norepinephrine over an 18-hr period. In addition, they measured blood glucose, indices of hepatic and renal function, lactate dehydrogenase as a general index of cellular injury, and plasma interleukin-1 β and nitric oxide levels. Upon euthanasia, thoracic aorta, lung, liver, and kidney were assayed for superoxide levels and lung and liver for expression of inducible nitric oxide synthase. Histology was performed on lung, liver, kidney, and aorta for evidence of neutrophil infiltration, and survival rates at 9 and 18 hrs were quantified. The investigators observed that HS infusion maintained mean arterial pressure in CLP rats with no effect on heart rate. In addition, HS infusion in these rats improved sys-

temic vascular reactivity and indices of organ and general cellular injury. Mechanistically, the investigators reported that HS attenuated the elevated levels of several mediators in both plasma (interleukin-1 β and nitric oxide) and tissues (superoxide). This translated into reduced neutrophil infiltration in lung and liver and 27% and 47% higher survival rates at 9 hrs and 18 hr, respectively, in CLP rats that received HS compared with normal saline. This study shows that in an animal model that may be the closest mimic available to human septic shock, 4 mL/kg HS was able to prevent hypotension, reduce organ dysfunction, and improve survival, possibly through its actions on hemodynamics and the inflammatory response.

Although this study has limitations regarding the clinical significance of the level of improvement seen with HS over normal saline, as well as the relevance of the results to human sepsis and septic shock, it does expand the therapeutic potential of HS in this field. Currently, a multicenter trauma trial sponsored by the U.S. National Institutes of Health and the U.S. Army is underway evaluating HS alone or with dextran compared with normal saline. Some of the enrolling centers are investigating the potential benefit of these hypertonic fluids on immune function and their ability to reduce multiorgan failure. The results of these studies are highly anticipated. Perhaps this study by Dr. Shih and colleagues (15) will encourage the planning of similar clinical studies to evaluate HS as the initial resuscitation fluid in the therapy of sepsis and septic shock, beyond its typical physiologic effects.

Michael A. Dubick, PhD
U.S. Army Institute of
Surgical Research
San Antonio, TX

REFERENCES

1. Velasco IT, Pontieri V, Rocha e Silva M Jr, et al: Hyperosmotic NaCl and severe hemorrhagic shock. *Am J Physiol* 1980; 239: H664–H673
2. Dubick MA, Bruttig SP, Wade CE: Issues of concern regarding the use of hypertonic/

*See also p. 1864.

Key Words: hypertonic saline; sepsis; hemorrhage; rats; inflammatory response

The author has not disclosed any potential conflicts of interest.

Copyright © 2008 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins

DOI: 10.1097/CCM.0b013e318176aabe

- hyperoncotic fluid resuscitation of hemorrhagic hypotension. *Shock* 2006; 25:321–328
3. Wade CE, Kramer GC, Grady JJ, et al: Efficacy of hypertonic 7.5% saline and 6% dextran-70 in treating trauma: A meta-analysis of controlled clinical studies. *Surgery* 1997; 122:609–616
 4. Olsson JSC: The use of hypertonic solutions in prehospital care in Scandinavia. *Scand J Trauma Resusc Emerg Med* 2004; 12:78–85
 5. Wade CE, Grady JJ, Kramer GC, et al: Individual patient cohort analysis of the efficacy of hypertonic saline/dextran in patients with traumatic brain injury and hypotension. *J Trauma* 1997; 42(5 Suppl):S61–S65
 6. Himmelseher S: Hypertonic saline solutions for treatment of intracranial hypertension. *Curr Opin Anaesthesiol* 2007; 20:414–426
 7. Luybaert P, Vincent JL, Domb M, et al: Fluid resuscitation with hypertonic saline in endotoxic shock. *Circ Shock* 1986; 20:311–320
 8. Kreimeier U, Frey L, Dentz J, et al: Hypertonic saline dextran resuscitation during the initial phase of acute endotoxemia: Effect on regional blood flow. *Crit Care Med* 1991; 19:801–809
 9. Horton JW, Walker PB: Small-volume hypertonic saline dextran resuscitation from canine endotoxin shock. *Ann Surg* 1991; 214:64–73
 10. Angle N, Hoyt DB, Coimbra R, et al: Hypertonic saline resuscitation diminishes lung injury by suppressing neutrophil activation after hemorrhagic shock. *Shock* 1998; 9:164–170
 11. Pascual JL, Ferri LE, Seely AJ, et al: Hypertonic saline resuscitation of hemorrhagic shock diminishes neutrophil rolling and adherence to endothelium and reduces in vivo vascular leakage. *Ann Surg* 2002; 236:634–642
 12. Pascual JL, Khwaja KA, Ferri LE, et al: Hypertonic saline resuscitation attenuates neutrophil lung sequestration and transmigration by diminishing leukocyte-endothelial interactions in a two-hit model of hemorrhagic shock and infection. *J Trauma* 2003; 54:121–130
 13. Ciesla DJ, Moore EE, Zallen G, et al: Hypertonic saline attenuation of polymorphonuclear neutrophil cytotoxicity: Timing is everything. *J Trauma* 2000; 48:388–395
 14. Junger WG, Liu FC, Loomis WH, et al: Hypertonic saline enhances cellular immune function. *Circ Shock* 1994; 42:190–196
 15. Shih CC, Chen SJ, Chen A, et al: Therapeutic effects of hypertonic saline on peritonitis-induced septic shock with multiple organ dysfunction syndrome in rats. *Crit Care Med* 2008; 36:1864–1872

Levo is in the air: Take a deep breath!*

Mrs. Fictive-Fitness is a 40-yr-old “healthy” woman who underwent a laparoscopic cholecystectomy that was complicated by iatrogenic intestinal perforation, necessitating a 10-cm bowel resection with end-to-end anastomosis. On the second postoperative day, she developed septic shock and required high doses of norepinephrine to maintain a sufficient mean arterial blood pressure. Despite a hemoglobin value of 10 g/dL and appropriate intravascular volume replacement, her central venous oxygen saturation was unacceptably low, so incremental doses of dobutamine were continuously infused with the aim to achieve threshold values of $\approx 70\%$. Although the surgical focus had been eliminated and antibiotic therapy was judged as appropriate, septic shock progressed. Probably due to adrenergic receptor down-regulation, excessive catecholamine doses were needed to maintain at least a minimal circulation. In the meantime, Mrs. Fictive-Fitness had undergone metamorphosis and converted into Mrs. Ultra-Weak-

ness. As she suffered from multiple organ failure despite (or because of?) having received 1 $\mu\text{g/kg/min}$ norepinephrine and 25 $\mu\text{g/kg/min}$ dobutamine, the intensive care physicians in charge considered administering levosimendan as drug of last resort, hoping that a somewhat “magic bullet” could revive her. Because she had severe myocardial insufficiency with a cardiac index of 1.5 L/min/m² and a central venous oxygen saturation of only 45%, the team decided to give a bolus dose of 24 $\mu\text{g/kg}$ body weight. Some minutes later, her mean arterial blood pressure dropped dramatically, and a couple of hours thereafter she was dead. What went wrong with this case?

In the last years, levosimendan has emerged as a promising agent in the management of reversible cardiovascular dysfunction. Levosimendan is a calcium sensitizer that reliably increases cardiac output at low energetic costs. Due to simultaneous activation of adenosine triphosphate-sensitive potassium channels, levosimendan contributes to global vasodilatation within the systemic and pulmonary circulation (1). Whereas the decrease in afterload may be desirable, the subsequent decrease in systemic vascular resistance may threaten organ perfusion. Therefore, it is important to guarantee both appropriate vascular filling and tone before levosimendan infusion. Since the vasodilatory properties are dose dependent, vasodilation is most pronounced if a bolus is given (without pre-

ceding volume loading and coadministration of a vasoconstrictor agent). But what do we do if the patient suffers from systemic inflammation, associated with pronounced vasodilatation in conjunction with pulmonary hypertension and right heart failure? In this life-threatening condition, it would be smart to administer an anti-inflammatory agent that ameliorates cardiopulmonary dysfunction without further deteriorating systemic hemodynamics and tissue perfusion.

In this issue of *Critical Care Medicine*, Dr. Boost and colleagues (2) report the results of a timely and carefully conducted study investigating the role of aerosolized levosimendan in the experimental setting of ventilator-induced lung injury (VILI) in rats. The authors demonstrated that nebulization of levosimendan, when applied preinjury, reduced the release of inflammatory mediators and improved survival. The data support the concept that prophylactic inhalation of levosimendan may be a useful option to prevent pulmonary derangement in ventilated subjects.

Previous studies provided evidence that among the factors involved in the pathogenesis of VILI, overdistension and collapse of distal bronchioli and alveoli during mechanical ventilation, as well as activation and release of proinflammatory mediators, play a pivotal role. In addition, increased expression of intercellular adhesion molecule-1, cytokine-induced neutrophil chemoattractant-1, and

*See also p. 1873.

Key Words: levosimendan; acute lung injury; ventilator-induced lung injury; sepsis; septic shock; hemodynamics

The authors have not disclosed any potential conflicts of interest.

Copyright © 2008 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins

DOI: 10.1097/CCM.0b013e318176aae9